REMARKS

At the outset, Applicants wish to extend their appreciation for the reconsideration and withdrawal of the finality of the Office Action. This decision is memorialized in the Interview Summary Form dated August 30, 2005. Applicants also wish to extend thanks to Supervisory Examiner Padmanabhan and Examiner Williams for their courtesies for the personal interview conducted on November 10, 2005.

The reconsideration and withdrawal of the rejection under §102(b) over the Castro publication are acknowledged and appreciated. One ground of rejection remains. Claims 16-38 have been rejected under §103(a) as being unpatentable over Castro, *et al.* (U.S. Patent 6,113,888, "*Castro*"), in view of Cooper, *et al.* (U.S. Patent 4,552,872, "*Cooper*"), in view of Quigley, *et* al. (U.S. Patent 6,075,056, "*Quigley*"), and further in view of Vollhardt, *et al.* (U.S. Patent 6,274,124, "*Vollhardt*"). *Castro* is alleged not to teach hydrocortisone acetate, triamcinolone acetate, and their respective percentages in the compositions, or butylene glycol or a mixture of butylene glycol and propylene glycol as additional solvents. *Cooper* is alleged to supply these teachings. *Quigley* is alleged to teach topical formulations that may be in the form of creams, ointments, gels, lotions, foams, powders, shampoos, and/or liquid solutions comprising a steroid (0.01-2.5 percent by weight) and a propylene glycol (5-20 percent by weight), wherein the steroid can be triamcinolone acetate. *Vollhardt* is alleged to teach cosmetic and/or dermatological formulations comprising 1, 2-pentanediol and at least one cosmetic or dermatological active agent in a cosmetically and/or pharmaceutically acceptable carrier for topical application to the skin, wherein the 1, 2-pentanediol should preferably be present in an amount of 0.5 percent to 6 percent by weight of the composition gives improved water resistance to the compositions as compared to 1,

2-propanediol and 1, 2-hexanediol, and wherein the cosmetic and/or dermatologically active agents include steroidal anti-inflammatory agents such as hydrocortisone, non-steroidal anti-inflammatory agents, anti-microbial agents and fragrances.

The Examiner has determined that it would have been obvious to use 1, 2-pentanediol in the topical pharmaceutical corticosteroid compositions of *Cooper*, in view of *Vollhardt*, as *Castro* demonstrated that 1,2-pentanediol could be combined with another diol (propylene glycol or butylene glycol or both), and that *Castro*, *Cooper*, *Quigley*, and *Vollhardt's* compositions all contain the same dermatologically active agents (steroidal anti-inflammatories). The increased water resistance properties of 1, 2-pentanediol-containing compositions would have motivated one of ordinary skill in the art to combine the compositions. A reasonable chance of success would have been expected as the compositions demonstrated that 1, 2-pentanediol can be combined with additional diols in all the compositions detailed including steroidal anti-inflammatory agents exemplified by hydrocortisone.

Applicants respectfully disagree with the determination that the claimed invention would have been obvious. *Cooper* and *Quigley* are the two cited publications that are most focused on topical delivery of steroidal anti-inflammatory agents such as hydrocortisone, teach formulating the agents with C3, C4 and/or C6 diols, but not the C5 diol pentylene glycol. The silence of these two publications with respect to pentylene glycol, considered in the context of their entire disclosures and the other cited prior art, would not have motivated persons skilled in the art to formulate hydrocortisone and its derivates with pentylene glycol. Thus, Applicants submit that the collective teachings of the cited prior art do not establish a case of *prima facie* obviousness. Regardless, the evidence of unexpected results contained in the

specification (and as elaborated upon in the Fares Declaration of record) would effectively rebut any such case.

Since the text of the rejection is virtually identical to the rejection set forth in the prior Office action, Applicants reiterate and incorporate herein by reference, the remarks set forth in their response dated March 29, 2005. The Examiner's rebuttal, set forth on pages 2-3 of the Office action, is that in *Castro,* it is known in the cosmetic arts to use hydrocortisone (and other active ingredients) in cosmetic formulations, and that pentylene glycol is a common cosmetic formulation ingredient. Additionally, *Castro* clearly demonstrates that the pentylene glycol can be used in the formulation of a variety of cosmetic compositions (specifically a mousse composition) with various other ingredients including alkyl glycols and solvents. The rebuttal also states that *Cooper* was used to reinforce that the hydrocortisone compounds -- - hydrocortisone acetate and triamcinolone acetate -- while generally taught in *Castro,* can readily be formulated into topical compositions in the presence of alkyl glycols, that *Quigley* was *simply* used to demonstrate that the alkyl glycols and hydrocortisone compounds could be formulated in a variety of embodiments, and that *Vollhardt* demonstrated that there were reasons to specifically use pentylene glycol in topical formulations as it imparted improved water resistance (emphasis added). These statements reflect that these references, particularly *Cooper* and *Quigley*, were not considered as a whole.

Applicants are not disputing that hydrocortisone and pentylene glycol have been disclosed in connection with cosmetic compositions. Applicants submit however that the collective teachings of the references would not have motivated a person skilled in the art to produce the claimed invention with a reasonable expectation of success. A reference should be considered as a whole, and portions arguing against or teaching

away from the claimed invention must be considered. *See, e.g., Bausch & Lomb, Inc. v. Barnes Hind/Hydrocurve, Inc.*, 796 F.2d 443, 230 U.S.P.Q. 416, 419 (Fed Cir. 1986) (reversing district court's holding of obviousness of the patent claims in suit, *inter alia*, on the ground that it impermissibly took a single statement in the prior art out of context by failing to consider it together with the remainder of the same paragraph and the following paragraph, and thus failed to gain a full appreciation of the prior art reference) (*quoting In re Mercer*, 515 F.2d 1161, 1165-66, 185 U.S.P.Q. 774, 778 (C.C.P.A. 1975) ("It is impermissible to pick and choose within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art.") In this case, the rejection is untenable because it fails to consider specific disclosures in the cited references that are believed to teach away from the claimed invention.

Cooper and his co-inventors discovered that a *select number* of combinations of a binary penetration system containing a cell-envelope disordering compound and a C3-C4 diol, previously thought to be useful only in delivering non-steroidal varieties of anti-inflammatory actives and select substituted adenosine- and guanine-derived anti-virals, could consistently and dramatically improve topical delivery of certain corticosteroids (*Cooper*, col., 3, lns. 1-12). Hydrocortisone and various derivatives are included among the agents whose penetration could be enhanced by such combinations. See, cols. 7-8. *Cooper* does not teach the C5 diol, pentylene glycol. In addition, none of the summaries of the prior art provided on cols. 3-4 of *Cooper* contains any mention of the C5 diol.

Quigley is directed to stable topical formulations containing an antifungal agent and an anti-inflammatory steroid.

Hydrocortisone is one of many steroids that are disclosed. See, col. 2, line 9, and col. 5, lns. 26 and 61. Among the excipients (*e.g.*, solvents, emollients, humectants and emulsifiers) disclosed on cols. 2-3 and elsewhere, there is no mention of pentylene glycol. On col. 7, lns. 65-7, *Quigley* teaches that with respect to the exemplified embodiments of his inventive compositions, "propylene glycol is a solvent and can be replaced by butylene glycol, hexylene glycol, polyethylene glycols, or polypropylene glycols." (This same statement also appears on col. 8, lns. 52-4 and col. 9, lns. 55-6.) This statement further appears on col. 2, lns. 55-6 in the broader context of pharmaceutical excipients that may be used in his invention. Pentylene glycol is noticeably absent from all of these disclosures. The fact that it is the only omission among the C3-C6 glycols prompts the conclusion that it was not a result of Cooper and Quigley simply not having tested pentylene glycol. This is more than mere silence -- it is a disincentive to formulate hydrocortisone with pentylene glycol. Thus, *Cooper* and *Quigley* provide no motivation to use pentylene glycol in combination with hydrocortisone for topical application, and if anything, teach away from use of a C5 diol.

At the interview, the Examiners explained that the collective teachings of two or more prior art references may establish *prima facie* obviousness even if the motivation for combining them differs from a particular problem that the claimed invention was designed to solve. Although this statement is correct as a general legal proposition, the fact remains that the collective teachings of *Castro*, *Cooper*, *Quigley* and *Vollhardt* do not establish *prima facie* obviousness. In the context of the presently claimed invention, the Examiners conceded that *Vollhardt's* motivation for formulating cosmetic and/or determatological active agents such as sunscreens with pentylene glycol, namely to enhance water resistance and thus

retention of the agent on the skin, differed from Applicants' goals, which as explained in the present specification and the Declaration by co-inventor Dr. Fares (submitted on March 29, 2005), were to increase penetration and bioavailability of hydrocortisone. Applicants submit that the claimed invention would not have been obvious, regardless of the different motivation provided by *Vollhardt*.

Quigley sought to enhance retention of the anti-inflammatory agent on the skin, and minimize penetration of the agent through the skin. (See, col. 2, lns. 23-6 of *Quigley*.) In contrast, *Cooper* desired enhanced transepidermal and percutaneous delivery of corticosteroids. However, the main thrust of *Vollhardt's* disclosure is directed to sunscreen agents, wherein enhanced water resistance makes perfect sense. See col. 2, lns. 59-62 of *Vollhardt* ("Accordingly, a major object of the present invention is the provision of novel cosmetic or dermatological compositions, in particular sunscreen compositions, which have increased water resistance.") In contrast, *Cooper* and *Quigley* were focused primarily on steroidal anti-inflammatory agents such as hydrocortisone. The point is that regardless of the motivation -- be it *Quigley's* retention or *Cooper's* penetration -- a person skilled in the art seeking to formulate hydrocortisone for topical application, would have been motivated to follow the teachings in *Cooper* and *Quigley* as opposed to *Vollhardt*, and would not have used pentylene glycol.

The Office action further states that the Fares Declaration was not convincing because while setting forth the reasoning as to why the applicant chose to use pentylene glycol and the effects noticed with the concurrent use of pentylene glycol with hydrocortisone, it did not set forth any argument as to why the pentylene glycol/hydrocortisone combination is patentable. Applicants are not aware of any rule or provision in the MPEP that requires a declarant to provide an "argument"

in favor of patentability. Contrary to the allegations in the Office action, Dr. Fares does in fact explain why he believes the claimed invention is patentable and he reiterates Applicants' position that the claimed invention achieves results that would not have been expected in view of the collective teachings of the cited prior art. These results, which flow from the unexpected discovery the hydrocortisone is more soluble in pentylene glycol than in other diols disclosed in the cited prior art, include greater aesthetic appeal, less tackiness and greater penetration and bioavailability. The evidence that establishes unexpected results is set forth in the specification. The MPEP is explicit as to how such evidence is to be treated. Objective evidence of secondary considerations, *e.g.*, unexpected results, is relevant to the issue of obviousness, and regardless of whether it is presented in the specification, by counsel or via affadavit or declaration, it must be considered in every case in which it is present, and that when evidence of any such secondary consideration is submitted, the examiner must evaluate the evidence. See, MPEP §2141(Rev. 3, August 2005 at 2100-125 and 158)(*citing In re Soni*, 34 U.S.P.Q.2d 1684, 1687 (Fed. Cir. 1996) (error not to consider evidence presented in the specification). Given that there is no statement in the Office action indicating that the evidence was considered, Applicants request consideration of the evidence along with this response.

As described in the present specification, the claimed invention achieves several unexpected results. These results flow from Applicants' discovery that hydrocortisone and its derivatives are more soluble in pentylene glycol than other polyols such as glycerol, propylene glycol, butylene glycol and hexylene glycol, which are the glycols taught in *Quigley* and *Cooper*. More specifically, as shown in Example 1 on page 11, Applicants discovered that hydrocortisone is about two times

more soluble in pentylene glycol than in hexylene glycol, about 1.5 times more soluble in pentylene glycol than in propylene glycol, and about 1.25 times more soluble in pentylene glycol than in butylene glycol. There are no teachings or suggestions in *Quigley* or *Cooper* to these effects. As taught in the present specification, there are at least three unexpected benefits that flow from the combination of pentylene glycol and hydrocortisone and its derivatives, namely aesthetic appeal, less tackiness and greater bioavailability. The first two advantages are described on pages 5-6 as follows:

> Due to the greater solubility of the active agents pentylene glycol, the amounts of the other solvents are significantly lower, e.g., about 20 to 95 percent less than if pentylene glycol were not present. Relatively high amounts of glycols are undesirable from several standpoints, especially in terms of aesthetic appeal and tackiness. In contrast, compositions of the present invention are more aesthetically acceptable and have less tackiness.

In Example 7 on pages 16-18 of the specification, Applicants compared the rate of release of hydrocortisone from various commercially available one percent hydrocortisone anti-itch creams and ointments. The results show that the release rate of hydrocortisone from a gel of the present invention was about 100 times greater than the commercial products, none of which contains pentylene glycol. As described in paragraph 34 on page 18, and illustrated in Fig. 1, the results also show that the compositions of the present invention provided greater availability of the active agent to penetrate the affected area on the skin or scalp, and thus provided greater bioavailability of the active agent.

As attested to by Dr. Fares, these results would not have been expected based on the collective teachings of the prior art. By specifically limiting the diols to C3, C4 and/or C6 diols, *Cooper* and Quigley are believed to teach away from the

claimed invention. *Vollhardt*'s primary objective was to increase water resistance or in other words, the amount of time that a sunscreen agent actually stays on the surface of the skin. *Vollhardt* does teach that his invention can also be practiced with antioxidants, anti-inflammatory compounds, anti-microbial compounds, antiperspirants, fragrances and skin whitening compounds. See columns 4-5. Hydrocortisone is thus merely one of many, many other of *Vollhardt's* less preferred active agents, leaving one skilled in the art to pick and choose from a myriad of combinations in order to arrive at the presently claimed invention.

In view of the foregoing, Applicants submit that to the extent *prima facie* obviousness has been properly established, the evidence of unexpected results weighs in favor of a determination of nonobviousness. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

As it is believed that all of the rejections set forth in the Official action have been fully met, favorable reconsideration and allowance are earnestly solicited.

If, however, for any reason the Examiner does not believe that such action can be taken at this time, it is respectfully requested that he/she telephone Applicants' attorney at (908) 654-5000 in order to overcome any additional objections that he might have.

If there are any additional charges in connection with this requested amendment, the Examiner is authorized to charge Deposit Account No. 12-1095 therefor.

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Respectfully submitted,

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